UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/697,186	10/27/2000	Sigeyuki Yokoyama	04853.0048	4446

22852 7590 09/10/2002

FINNEGAN, HENDERSON, FARABOW, GARRETT &
DUNNER LLP
1300 I STREET, NW
WASHINGTON, DC 20006

EXAMINER	
KERR, KATHLEEN M	
ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 09/10/2002 14

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/697,186	YOKOYAMA ET AL.	
	Examiner	Art Unit	
	Kathleen M Kerr	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) *4-9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Application Status

1. In response to the previous Office action, a written restriction requirement (Paper No. 12, mailed on May 30, 2002), Applicants filed an election received on July 1, 2002 (Paper No. 13). Claims 1-9 are pending in the instant Office action.

Election

2. Applicants' election with traverse of Group I, Claims 1-3 in Paper No. 13 is acknowledged. The traversal is on the ground(s) that "it would not be an undue burden on the Office to search the art concerning Groups I, II and III at one time" because the mutant proteins and DNA sequences are related, because the subject matter falls within a single classification, and because there are a limited number of claims in the application. These arguments are not found persuasive for the following reasons. The search for mutant protein sequences is performed in wholly distinct sequence databases wherein protein sequences are compiled. A search of Group II could require searching in DNA databases, a search that is not co-extensive with the elected Group. Any additional search that is not co-extensive with the search of the elected claims is considered burdensome on the Examiner. While Groups I-III fall within the same classification, their subclasses are wholly distinct and would require separate searching. Lastly, Applicants' arguments concerning the limited number of claims are not persuasive because the burden of the search is not affected by the number of claims, but by the scope they encompass.

The requirement is still deemed proper and is therefore made FINAL. Claims 1-9 are pending in the instant application. Claims 4-9 are withdrawn from consideration as non-elected inventions. Claims 1-3 will be examined herein.

Priority

3. The instant application is granted the benefit of priority for the foreign application 309616/1999 filed in Japan on October 29, 1999 as requested in the declaration. Receipt is acknowledged of papers submitted under 35 U.S.C. § 119(a)-(d), which papers have been placed of record in the file. No translation of the priority document, filed in Japanese, has been filed

Information Disclosure Statement

4. The information disclosure statement filed on June 22, 2001 (Paper No. 5) has been reviewed, and its references have been considered as shown by the Examiner's initials next to each citation on the attached copy.

Drawings

5. The drawings are considered informal for the reasons detailed in the attached copy of PTO Form 948. Appropriate correction is required in response to the instant Office action and may not be held in abeyance (see 37 C.F.R. § 1.85(a)).

Objections to the Specification

6. In the specification, the Abstract is objected to for not completely describing the disclosed subject matter (see M.P.E.P. § 608.01(b)). It is noted that in many databases and in foreign countries, the Abstract is crucial in defining the disclosed subject matter, thus, its

completeness is essential. The Examiner suggests the inclusion of a reference to the kanamycin resistance gene from *Staphylococcus aureus* for completeness. Also, complete sentences are required for clarity.

7. The specification is objected to for being confusing with respect to the sequence listing. The sequence listing contains 20 sequences. Every SEQ ID NO is mentioned in the specification and/or the claims except SEQ ID NOs: 12-20. It is unclear why said sequences are in the sequence listing if they are not described in the specification. All SEQ ID NOs in the sequence listing must be described in the specification. Appropriate correction is required.

Claim Objections

8. Claim 3 is objected to under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The instant objection is only relevant in light of Interpretation A below of Claim 1. SEQ ID NO:3 has all nine point mutations noted in Claim 1 plus nine additional mutations. This scope does not further limit SEQ ID NO:1 with only up to all nine point mutations (as found in Interpretation A). Appropriate amendment to Claim 3, and/or optionally Claim 1, is required.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1 and 3 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The scope of Claim 1 can be interpreted in at least two reasonable ways: Interpretation A encompasses SEQ ID NO:1 with any one or more of the nine point mutations listed with *no other changes*; and Interpretation B encompasses any kanamycin nucleotidyltransferase (KNT) having any one or more of the nine point mutations relative to SEQ ID NO:1 and optionally *any other mutations* in the sequence.

Interpretation A is problematic in light of Claim 3, which is drawn to a sequence that is SEQ ID NO:1 with all nine point mutations plus additional mutations. See Claim Objections above. However, this interpretation is a reasonable one considering the claim language, particularly the term "point mutations". In the art, point mutations are typically specified and are the *only* mutations in a sequence. If this is the intended scope, Claim 3 should be rewritten as an independent claim and Claim 1 should be rewritten to clearly identify SEQ ID NO:1 with up to the nine point mutations as follows: ---having the sequence of SEQ ID NO:1 with one or more point mutations selected from the group consisting of ... and having improved thermostability---.

Interpretation B is problematic for several reasons. The phrase "as against...SEQ ID NO:1" is clear when only the nine noted point mutations are allowed; however, when the scope encompasses any number of other mutations in the sequence, the corresponding residues are difficult to clearly discern, especially in the absence of a pile-up of several KNT sequences.

Moreover, what limitation does the word "mutant" provide? If a naturally occurring KNT sequence has a leucine at position 57 (relative to SEQ ID NO:1), would this meet the limitations of the claim? The Examiner notes that the instant claims are product claims; thus the initial Met residue at position 57 would seem to be irrelevant to the final "mutant" product that has a Leu in this position. For all of the above reasons, the scope of Claim 1 is unclear and the language of Claims 1 and 3 is unclear. Appropriate amendment is required.

10. Claims 1-3 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "improved thermostability" in Claims 1 and 2 is unclear. On page 6 of the instant specification, "improved thermostability" is defined as "the retention of enzyme activity under such high temperature conditions that the wild type protein would be denatured and the enzyme activity would be lost." In Figure 2, thermostability is measured by both structural retention (CD spectra) and enzyme activity after a defined heat treatment; the temperature at which structural stability and enzyme activity break down is consistent between these assays. However, the nature of the "wild type" enzyme (i.e., the reference point) in the instant claims is unclear. In Claims 1 and 3, SEQ ID NO:1 is implied as a reference; in Claim 2, no reference is mentioned. In the instant application, a naturally occurring, wild type *S. aureus* kanamycin nucleotidyltransferase (KNT) is disclosed as SEQ ID NO: 11 (WT). Additionally, a well characterized, heat stable KNT mutant (D80Y and T130K with respect to WT) is disclosed as SEQ ID NO:1 (WT*). Throughout the specification, both WT and WT* are used as references points for the "improved thermostability" of the disclosed mutants. The standard, to

which "improved thermostability" should be compared, is wholly unclear. Appropriate clarification is required.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claim 1 rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant rejection is based solely on Interpretation B above of the scope of Claim 1.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical

characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

In the instant specification, kanamycin nucleotidyltransferases (KNTs) are described by way of *S. aureus* sequences, wherein the wild-type is SEQ ID NO:11 and a WT* (well known thermostable mutant) is SEQ ID NO:1. By virtue of Interpretation B above, any KNT having any structure is encompassed by the claimed scope. Such proteins are only described by limited functional characteristics, which do not include a rationale for thermostability; no structural relationship is described among other KNT species or is used in the claims. Thus, one of skill in the art would be unable to predict the structure of other members of this genus by virtue of the instant disclosure. Therefore, claims drawn to KNTs without any specific structure are not adequately described.

12. Claim 1 is rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for kanamycin nucleotidyltransferases (KNTs) having the sequence of SEQ ID NO:1 with the exception of any one or more of the nine point mutations listed in Claim 1, does not reasonably provide enablement for KNTs having any sequence while retaining catalytic activity and improving thermostability. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The instant rejection is based solely on Interpretation B above of the scope of Claim 1. The amount of experimentation required of one of skill in the art to use the claimed invention to the full extent of its scope is undue.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a prima facie case is discussed below.

The instant specification presents no guidance or working examples of the production of KNTs that have such low sequence identity with respect to SEQ ID NO:1 and that have improved thermostability other than the random means of "directed evolution". The variety of structures within the scope of the claim is virtually boundless except for the point mutation limitation, which is unclear. The nature of the invention is such that the KNT is a functional protein useful in the degradation of kanamycin; and with such an unlimited deviation from a known sequence, the predictability of functionality becomes extremely low. Moreover, the

cause-and-effect relationship between improved thermostability and linear, amino acid structure is described in the specification using random (unpredictable) mutagenesis methods – no link between structure and function is described. Such enormous breadth and unpredictability renders the instant claims not enabled to the full extent of their scope without undue experimentation.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 1-3 are rejected under 35 U.S.C. § 102(a) as being anticipated by Hoseki *et al.* (IDS Paper No. 5 reference). The instant claims are drawn to SEQ ID NOs: 2 and 3 that are kanamycin nucleotidyltransferases (KNTs).

Hoseki *et al.* teach KNT mutants KT3-11 and HTK that are SEQ ID NOs: 2 and 3, respectively.

The Examiner notes that Hoseki *et al.* was published in November, 1999, a date less than a year before the filing date but after the claimed foreign priority date. Without a translation of the foreign priority document (submitted in Japanese), the Examiner must apply this intervening art. The Examiner suggests filing a translation of the Japanese priority document to overcome this art rejection.

14. Claim 1 is rejected under 35 U.S.C. § 102(b) as being anticipated by Matsumura *et al.* (IDS Paper No. 5 reference). The instant claim is drawn to a kanamycin nucleotidyltransferase (KNT) having the sequence of SEQ ID NO:1 except for at least a point mutation that is Ala62Val.

Matsumura *et al.* teach the *S. aureus* wild-type (SEQ ID NO:11) KNT enzyme having any one of more of several point mutations, particularly Ala62Val, induced by hydroxylamine treatment of the gene (see page 15302, Figure 4).

Other Art of Interest

15. The following are references considered pertinent to the patentability of the pending claims; however, as not sufficient to sustain art rejections:

a) Matsumura *et al.* (Single amino acid replacements affecting the thermostability of kanamycin nucleotidyltransferase. Molecular General Genetics (MGG) 1986 204:355-358) teach several point mutations for the enhancement of thermostability (see page 356, Table 1) but not the specific mutations delineated in Claim 1.

Conclusion

16. Claims 1-3 are rejected. for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (703) 305-1229. The examiner can normally be reached on Monday through Friday, from 8:30am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

KMK
September 9, 2002